CURRENT PROGRESS

Current Views on the Pathogenesis and Etiology of Rheumatoid Arthritis

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ABOUT 1% of the population of this country has rheumatoid arthritis and approximately 50% of these patients have significant disability; consequently there are roughly 100,000 people in Canada partially disabled by this disease. It is not surprising therefore that the understanding of rheumatoid arthritis is a major aim of research in the rheumatic diseases.

At first glance it might seem that we are no further along the road than we were 10 years ago, and indeed we have to admit that we are still ignorant of the cause of the condition and thus unable to cure it. Nevertheless in spite of this discouraging admission, we now have a much clearer sense of direction than we did a decade ago, and we can chart a course which we have grounds to hope will lead to the basic cause.

Firstly, we can now state that environmental considerations take precedence over genetic factors in the development of the disease. Studies of identical twins have clearly established that the disease may quite often be found in only one of a pair of identical twins,[1] from which we may conclude that heredity does not play the major etiological role. Earlier studies showing familial aggregation of cases of rheumatoid arthritis are now considered to be explicable by the statistical basis of the sampling methods, or alternatively on environmental influences common to the family, giving a "pseudo-genetic" pattern. (Examples of pseudo-genetic transmission of disease may be found in the vertical transmission, from parent to offspring, of viral neoplasia in experimental animals, and in the transmission of the unusual "degenerative" neurological disease, kuru, by the cannibalistic habits of the primitive natives of the Fore tribe in New Guinea.[2])

The exclusion of a genetic influence from primary causation does not, of course; eliminate the possibility that the hereditary constitution of the host does have some role in the pathogenesis of the disease. One could cite innumerable examples of the contributory participation of genetics, such as the susceptibility to rheumatic fever of a few patients out of the much larger number suffering from identical sore throats during an epidemic of streptococcal infection.

In the human, there are two unmistakable instances of a genetic effect contributing to rheumatoid arthritis, and both are examples of immunological deficiency. The first of these is the sex-linked recessive agammaglobulinemia which is associated with a high incidence of rheumatoid arthritis and other connective-tissue diseases. In this disease the genetically determined plasma cell deficiency, due to failure of development of the "gut-associated" lymphoid tissue, predisposes the affected boys to rheumatoid arthritis. The second example is a sibship of three girls in Vancouver who have a mild form of "chronic granulomatous disease of childhood" where there is a genetically determined failure on the part of the polymorphonuclear leukocytes to kill phagocytosed bacteria. Two of the girls have classical rheumatoid arthritis with subcutaneous nodules and the third has had recurrent episodes of arthritis which could be classified as probable rheumatoid arthritis. Therefore genetics may, through a number of distinct mechanisms, determine the response of the host to the etiological agent provided by the environment, and it is even possible that this agent is common or ubiquitous and that the presence or absence of disease is determined mainly by the host's constitution.

STAGES IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

The stages in the pathogenesis of rheumatoid arthritis may be represented schematically as shown at the top of page 148.

The patient's complaints and disability relate to the inflammatory process in the joints, and the mechanisms involved in the inflammatory reaction itself are probably little different in rheumatoid arthritis from those in any other inflammatory disease. The vasoactive amines, histamine, serotonin, bradykinin and other kinins,

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Etiological antigen → Immunopathological reaction → Inflammatory lesion → Pain and swelling

together with others we do not yet know, determine the vascular reaction. The release of these amines and the production of leukotoxins are presumably the consequence of both granulocyte and mast cell activity or dissolution. Mast cells, basophils and eosinophils probably contribute by active secretion of specific substances, whereas the polymorphonuclears are more likely to activate physiologically inactive precursors through their own non-specific proteolytic lysosomal enzymes. Research into the mechanism of inflammation may improve patient care through the discovery of better anti-inflammatory drugs or the synthesis of inhibitors to the vasoactive amines.

EVIDENCE FOR IMMUNOPATHOLOGY IN RHEUMATOID ARTHRITIS

Over the past 15 years the immunological aspects of rheumatoid arthritis have dominated research. The evidence in favour of a major role for immunopathology in the disease can be summarized in the following way:

Serological —Rheumatoid factor
—High gamma-G globulin levels
Histological—Plasmacytosis of bone marrow
—Infiltration of synovium by "immune cells" (lymphocytes, plasma cells, lymphoid follicles)

The 19 S macroglobulin, rheumatoid factor, is now identified as an immunoglobulin with the specific property of reacting with 7 S gammaglobulin. The production of rheumatoid factor is thought to be a secondary response to prolonged antigenic stimulation, probably by any one of many antigens, and it can be elicited in several animal species by experimental hyperimmunization with a variety of antigens. In humans, rheumatoid factor is found in subacute bacterial endocarditis and in a number of other chronic infections which provide prolonged antigenic stimulation to the patient's lymphoid tissue.

Serological evidence for prolonged immunological stimulation in rheumatoid arthritis is also seen in the high immunoglobulin G levels which are usually present. Histological support for such a mechanism is provided by the increased number of plasma cells in the bone marrow and also by the pathology of the involved joint. The rheumatoid synovium, in fact, resembles a lymph node undergoing antigenic stimulation, the cellular infiltrate being primarily lymphocytes and plasma cells, together with lymphoid follicles.

There can be little argument against the hypothesis that the etiological agent in rheumatoid arthritis provides a prolonged and marked antigenic stimulus.

The question of the relationship between the immunological reaction and the inflammatory reaction has recently evoked interesting laboratory observations. Hollander and Rawson[3] of Philadelphia noted that the polymorphonuclear leukocytes in the rheumatoid synovial fluid contained complexes of 19 S rheumatoid factor with 7 S immunoglobulin. The demonstration of these was possible through the employment of fluorescent staining with anti-human IgM and IgG antisera. Hollander postulated that the act of phagocytosis of these complexes stimulated the lysosomes of the leukocytes and the release of lysosomal enzymes produced the inflammatory reaction, as described above. Hollander then demonstrated that if purified IgG (3 mg.) from a rheumatoid arthritic patient was injected into the joint of the same patient, provided he was a rheumatoid-factor-positive case of rheumatoid arthritis, an acute inflammatory reaction would result. Subsequent work has demonstrated that if the Fc fragment of IgG is used, even smaller amounts, as low as 0.1 mg., will induce acute attacks in rheumatoid patients. The Fc fragment can be obtained either from a rheumatoid or non-rheumatoid subject, and the acute inflammation will result in any rheumatoid-factor-positive rheumatoid patient provided that the genetic type of the Fc fragment is the same as that of the patient. This work may be summarized as shown at the foot of this page.

The part that complement may play in the observations of Hollander and Rawson has not yet been clarified. There is no doubt, however, about the importance of complement in the pathogenesis of other lesions seen in some connective tissue diseases. The glomerular and arteritic lesions present in some systemic connective-tissue diseases are almost certainly

3 mg. patient's own IgG → Patient's knee → Inflammation, if patient has rheumatoid factor

0.1 mg. Fc fragment of IgG from normal or R-A patient → Knee of subject of same genetic type of γ-globulin → Inflammation, if recipient has rheumatoid factor

induced by the irritant properties of the "later" components of complement, activated by the antigen-antibody complex. To what extent the inflammatory lesions of rheumatoid arthritis are precipitated by complement is not yet defined, but the fact remains that the serum complement level in arthritis is normal or elevated while the synovial fluid level is considerably reduced when the synovitis is active.

These observations provide hypothetical mechanisms whereby the immunopathological reaction characteristic of rheumatoid arthritis might bring about an inflammatory response. They have stimulated research in these areas, but it is too early to assess the contribution of this work to the elucidation of the basis of rheumatoid arthritis. It has to be remembered that typical rheumatoid arthritis can occur in the absence of rheumatoid factor, both in adults and children, and particularly in agammaglobulinemic boys. Moreover, the injection of rheumatoid factor into normal individuals does not cause arthritis.

Definition of the immunopathogenesis of the rheumatoid inflammation may provide therapeutic opportunities through immunosuppressive therapy. However, at this time, the known and unknown hazards of immunosuppression prohibit its use except in the most unusually severe cases of rheumatoid arthritis.

ROLE OF PRIMARY INFECTIVE ANTIGEN

Research is currently being conducted based on the hypothesis that a primary infective antigen is the etiological agent in rheumatoid arthritis. Within the past few years the study of a number of animal diseases of viral origin has revealed mechanisms that might well apply to human rheumatoid arthritis. Concepts vary according to the interests of the worker and the prevailing popular trend at the particular time, and the present author is microbiologically orientated.

N.Z.B. DISEASE OF MICE

In 1959 New Zealand researchers[4] noted that the members of a strain of New Zealand black mice died early in life and that death was associated with renal disease, hemolytic anemia and the presence of antinuclear factors in the serum. It was recognized that this disease had many features in common with disseminated lupus in humans, and its restriction to a single strain suggested a genetic determination. Intensive investigation has not yet clarified the picture and there is still dispute over "facts" and interpretations. Nevertheless there seems to be general agreement that the renal disease is of the "antigen-antibody-complex type" and is morphologically similar to the lesions of disseminated lupus and streptococcal glomerulonephritis. The nature of the antigen and the antibody which form the complexes is debated; one view holds that the complex is nuclear antigen combined with antinuclear factors, while the other believes that viral antigens are combined with viral antibody and deposited in basement membrane.

Recently the genetic hypothesis has tended to be displaced by a pathogenesis based on chronic viral infection. Shulman *et al.*[5] observed that the incidence of N.Z.B. disease in colonies of these mice varied markedly in different locations. Thus the Bar Harbour strain had a high incidence of the disease, whereas in a colony from Tennessee the incidence was low; the two N.Z.B. strains were proved to be genetically identical by cross-skin grafting. This observation was clearly more compatible with an environmental rather than a genetic cause.

Mellors[6, 7] has provided strong evidence to support the viral etiology of N.Z.B. disease. He has consistently found viral particles by the electron microscope in the tissues of involved animals, and has transferred the disease to Swiss mice by inocula containing these viral particles; the disease has appeared in 20% of the inoculated animals. He has used fluorescent and complement-fixing antibody studies to relate viral antigens to the disease.

The viruses concerned appear to be similar to the oncogenic C-type viruses found in several animal species, and in fact, N.Z.B. mice tend to develop reticulum cell sarcomas and pleomorphic lymphomas. Mellors postulates that this agent is transmitted vertically from parent to offspring and persists throughout the animal's life. Antibodies formed against specific antigens of the virus are thus responsible for the hemolysis and glomerulonephritis, through the membrane damage inflicted by complexes of antigen, antibody and complement. There is evidence that N.Z.B. mice may be immunologically hyperreactive, in that they develop higher antibody levels than other mouse strains when immunized by standard regimens. This peculiarity may explain their susceptibility to the disease in contrast to other strains of mice also harbouring latent oncogenic viruses without the development of such immunological syndromes.

LYMPHOCYTIC CHORIOMENINGITIS (LCM) VIRUS INFECTION IN MICE

The production of immunological lesions through a process of chronic viral infection is

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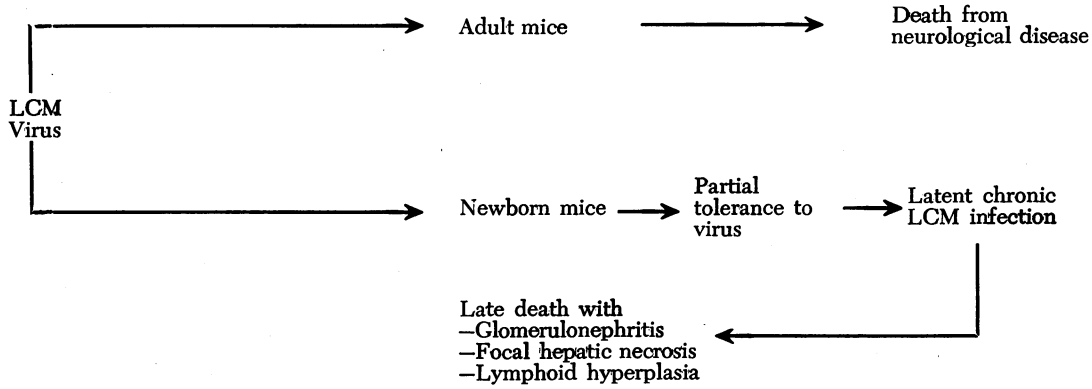
also well illustrated by lymphocytic choriomeningitis (LCM) infection of mice.[8-10] In the late 1930's Traub and subsequently Burnet and Fenner observed that the inoculation of adult mice with LCM virus would rapidly cause death from cerebral infection. However, if mice were inoculated with LCM on the first day of life, so that they became immunologically tolerant of the virus, they remained healthy even though the virus multiplied and a state of chronic viral infection ensued. These events may be set forth semi-diagrammatically thus:



The implication of this observation is that it is not the virus itself that causes the disease but the immunological reaction of the host to the virus. Nevertheless, if these latently infected mice are observed throughout their lives, they are often found to succumb to chronic glomerulonephritis, and show lesions of focal hepatic necrosis and lymphoid hyperplasia. Some strains of mice show a 100% incidence of these lesions within three months, while others show no manifestations at all of such a disease. It is notable that the N.Z.B. strain will develop severe renal disease when chronically infected with LCM virus in this manner, as well as antinuclear factors in their sera. Both the virus associated with N.Z.B. disease and the LCM virus are RNA viruses and therefore the presence of antinuclear factors cannot be explained on a simple basis of foreign DNA. The LCM virus can be found circulating in the blood as a complex with antibody and these complexes are deposited in the basement membrane, so that eluates of renal tissue contain LCM antigen.

ALEUTIAN MINK DISEASE

A disease that is at present arousing intense interest is Aleutian mink disease, first described in the late 1950's;[11-15] although it was first noted in the Aleutian strain of mink, it has subsequently been induced in other mink and also in ferrets. Arteritis, glomerulonephritis and hypergammaglobulinemia are the characteristic features of this disease, which is a serious economic threat to mink ranchers. The infection tends to remain latent in the colony but may suddenly assume epidemic proportions if the general health of the colony is depressed by other factors.

The marked hypergammaglobulinemia is of particular interest. It is initially heterogeneous in type, but as the disease progresses the IgG becomes homogeneous and may finally become monoclonal. The agent appears to multiply in macrophages, and both the spleen and liver are favoured sites. In the serum the agent circulates as a complex with IgG, but the latter does not appear to neutralize the agent and these complexes are infective. The renal lesions are of the "complex" type and the complexes can be demonstrated in renal tissue eluates. It has been claimed that the Aleutian mink agent is of such a small size that it cannot be a virus. It has not been cultivated *in vitro* and up to the present there seems to be no definite evidence that it is other than a very small virus with considerable resistance to physical and chemical inactivation when compared to other viruses.

POSSIBLE MECHANISMS FOR PRODUCTION OF IMMUNOPATHOLOGY

The above discussion indicates that the study of chronic viral infection and viral neoplasia in animals may be highly relevant to the understanding of rheumatoid arthritis and the other connective-tissue diseases. The production of pathological lesions through immunopathogenesis would seem to be due to one of three mechanisms. The first of these is the harmful effect of complexes formed by antigen, antibody and complement, the actual lesions depending on the localization of the complexes. Or there may be the development of a "delayed hypersensitivity

reaction" to the etiological antigen itself. A third alternative is the direct lymphocytotoxic effect characteristic of homograft rejection, and this presumably occurs only when an antigen recognized as foreign by the host's lymphocytes exists on the host's cell membrane.

There are a number of ways in which tissue antigens of the host might become antigenic and elicit a homograft rejection. Some interesting possibilities are as follows:

At the present time the prevailing view of the pathogenesis of rheumatic fever is that one of the antigens of the streptococcal cell wall is similar to a sarcolemma antigen on fibres of cardiac and arterial smooth muscle. The patient's reaction to this streptococcal antigen causes an immunological attack on his own sarcolemma antigen, resulting in myocarditis and arteritis. Other such examples of a cross-antigenicity between infecting micro-organisms and host tissues may be discovered in the future.

A second way in which host tissue could initiate an immune reaction is by undergoing antigenic alteration from the action of some environmental influence, whether physical, chemical or microbiological; this situation would be analogous to contact dermatitis elicited by the application of simple chemical substances or haptens. This concept has been developed by Lawrence[16] as the "self + X" hypothesis for the explanation of delayed hypersensitivity and these altered antigens are assumed to be susceptible to attack by the host's own lymphocytes. In considering tissues inside rather than on the surface of the host, one would expect that the synovium would be more liable to alteration by microbiological agents than by chemicals, and therefore the former might constitute the basic etiological factor in this type of response.

A third possibility is that an infecting virus may, during its multiplication, incorporate host antigens into its structure. For example, in the multiplication cycle of myxoviruses condensations of viral RNA appear beneath the host cell membrane. The viral RNA then forms a protuberance and finally a new virus particle is budded off. There is a strong probability that some host cell membrane is incorporated into the protein envelope which surrounds the viral RNA. If such proves to be the case, it would not be difficult to imagine the development of immunological reactions involving both the infecting virus and cell membrane antigen of the host's tissue.

REFERENCES

1. O'BRIEN, W. M.: *Arthritis Rheum.*, **11**: 81, 1968.
2. GAJDUSEK, D. C.: *New Eng. J. Med.*, **276**: 392, 1967.
3. HOLLANDER, J. L. AND RAWSON, A. J.: *Bull. Rheum. Dis.*, **18**: 502, 1968.
4. BIELSCHOWSKY, M., HELYER, B. J. AND HOWIE, J. B.: *Proc. Univ. Otago Med. Sch.*, **37**: 9, 1959.
5. SHULMAN, L. E. *et al.*: *Arthritis Rheum.*, **7**: 753, 1964 (abstract).
6. MELLORS, R. C. AND HUANG, C. Y.: *J. Exp. Med.*, **126**: 53, 1967.
7. MELLORS, R. C., AOKI, T. AND HUEBNER, R. J.: *J. Exp. Med.*, **129**: 1045, 1969.
8. HOTCHIN, J. E.: *Sympos. Quant. Biol.*, **27**: 479, 1962.
9. OLDSTONE, M. B. AND DIXON, F. J.: *Science*, **158**: 1193, 1967.
10. *Idem.*: *J. Exp. Med.*, **129**: 483, 1969.
11. HARTSOUGH, G. R. AND GORHAM, J. R.: *National Fur News*, **28**: 10, 1956.
12. HELMBOLDT, C. F. AND JUNGHERR, E. L.: *Amer. J. Vet. Res.*, **19**: 212, 1958.
13. PORTER, D. D., DIXON, F. J. AND LARSEN, A. A.: *J. Exp. Med.*, **121**: 889, 1965.
14. PORTER, D. D.: Aleutian mink disease. Paper presented at the Arthritis Foundation Research Conference: Atypical virus infections—possible relevance to animal models and rheumatic disease, Atlanta, Ga., December 28, 1968.
15. GORDON, D. A., FRANKLIN, A. E. AND KARSTAD, L.: *Canad. Med. Ass. J.*, **96**: 1245, 1967.
16. LAWRENCE, H. S.: *Physiol. Rev.*, **39**: 811, 1959.